**NEO-FRADIN - neomycin sulfate solution**
X-Gen Pharmaceuticals Inc.

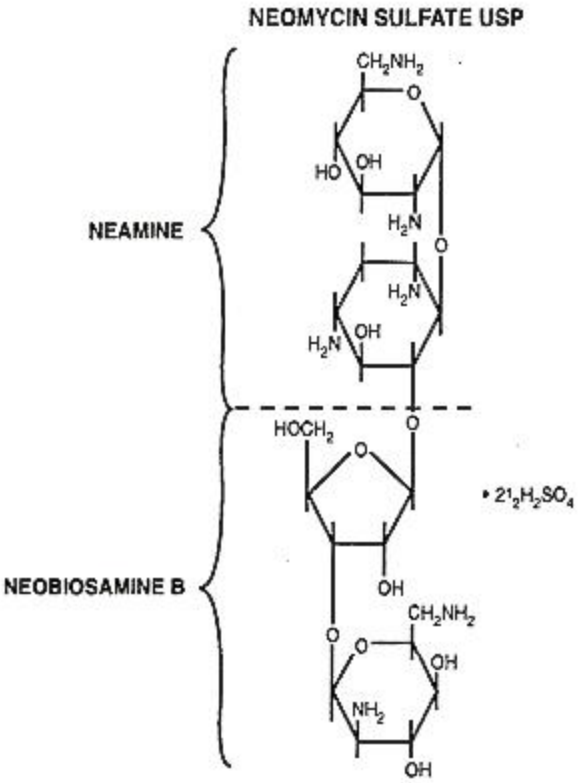
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Neomycin Sulfate Oral Solution and other antibacterial drugs, Neomycin Sulfate Oral Solution should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**BOXED WARNING**

**SYSTEMIC ABSORPTION OF NEOMYCIN OCCURS FOLLOWING ORAL ADMINISTRATION AND TOXIC REACTIONS MAY OCCUR. Patients treated with neomycin should be under close clinical observation because of the potential toxicity associated with their use**
**NEUROTOXICITY (INCLUDING OTOTOXICITY) AND NEPHROTOXICITY FOLLOWING THE ORAL USE OF NEOMYCIN SULFATE HAVE BEEN REPORTED, EVEN WHEN USED IN RECOMMENDED DOSES. THE POTENTIAL FOR NEPHROTOXICITY, PERMANENT BILATERAL AUDITORY OTOTOXICITY AND SOMETIMES VESTIBULAR TOXICITY IS PRESENT IN PATIENTS WITH NORMAL RENAL FUNCTION WHEN TREATED WITH HIGHER DOSES OF NEOMYCIN AND/OR FOR LONGER PERIODS THAN RECOMMENDED. Serial, vestibular, and audiometric tests, as well as tests of renal function, should be performed (especially in high risk patients).**
**THE RISK OF NEPHROTOXICITY AND OTOTOXICITY IS GREATER IN PATIENTS WITH IMPAIRED RENAL FUNCTION. Ototoxicity is often delayed in onset and patients developing cochlear damage will not have symptoms during therapy to warn them of developing eighth nerve destruction and total or partial deafness may occur long after neomycin has been discontinued.**
**Neuromuscular blockage and respiratory paralysis have been reported following the oral use of neomycin. The possibility of the occurrence of neuro-muscular blockage and respiratory paralysis should be considered if neomycin is administered, especially to patients receiving anesthetics, neuro-muscular blocking agents such as tubocurarine, succinylcholine, decamethonium, or in patients receiving massive transfusions of citrate anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena but mechanical respiratory assistance may be necessary.**
**Concurrent and/or sequential systemic, oral, or topical use of other aminoglycosides including paromomycin and other potentially nephrotoxic and/or neurotoxic drugs such as bacitracin, cisplatin, vancomycin, amphotericin B, polymyxin B, colistin, and viomycin should be avoided because the toxicity may be additive.**
**Other factors which increase the risk of toxicity are advanced age and dehydration.**
**The concurrent use of neomycin with potent diuretics such as ethacrynic acid or furosemide should be avoided since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance neomycin toxicity by altering the antibiotic concentration in serum and tissue.**

## DESCRIPTION

NEO-FRADIN Oral Solution for oral administration contains neomycin which is an antibiotic obtained from the metabolic products of the actinomycete *Streptomyces fradiae*. The pH range is 5.0 to 7.5. NEO-FRADIN Oral Solution is a clear orange solution with a cherry flavor. Each 5 mL of NEO-FRADIN Oral Solution contains 125 mg of neomycin sulfate (equivalent to 87.5 mg of neomycin). Inactive ingredients: benzoic acid, FD&C yellow no. 6, cherry flavor, glycerin, methylparaben, proplyparaben, sodium phosphate dibasic heptahydrate, sulfuric acid, diatomaceous earth, and purified water.
Sodium phosphate dibasic heptahydrate and sulfuric acid are used as pH adjusters.
The chemical name for Neomycin is: *0*-2, 6-diamino-2, 6-dideoxy-α-D-lucopyranosyl-(1#3)- *0*β-D-ribofuranosyl-(1#5)*0*-[2, 6-diamino-2, 6-dideoxy-α-D-glucopyranosyl-(1#4)]-2-deoxy-D-streptamine.
Neomycin B is identical except that the -α-D-glucopyranosyl residue in the neobiosamine moiety is β-L-idopyranosly.
The molecular weight of Neomycin is 614.67. The structural formula is represented below:




**NEOMYCIN B SULFATE $C_{23}H_{46}N_6O_{13} \cdot 2\frac{1}{2}H_2SO_4$**

## CLINICAL PHARMACOLOGY

Neomycin sulfate is poorly absorbed from the gastrointestinal tract. The small absorbed fraction is rapidly distributed in the tissues and is excreted by the kidney in keeping with the degree of kidney function. The unabsorbed portion of the drug (approximately 97 percent) is eliminated unchanged in the feces.

Growth of most intestinal bacteria is rapidly suppressed following oral administration of neomycin sulfate, with the suppression persisting for 48-72 hours. Nonpathogenic yeasts and occasionally resistant strains of *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*) replace the intestinal bacteria.

As with other aminoglycosides, the amount of systemically absorbed neomycin transferred to the tissues increases cumulatively with each repeated dose administered until a steady state is achieved. The kidney functions as the primary excretory path as well as the tissue binding site with the highest concentration found in renal cortex. With repeated dosings, progressive accumulation also occurs in the inner ear. Release of tissue bound neomycin occurs slowly over a period of several weeks after dosing has been discontinued. Protein binding studies have shown that the degree of aminoglycoside protein binding is low and, depending upon the methods used for testing, this may be between 0 and 30 percent.

### Microbiology

*In vitro* tests have demonstrated that neomycin is bactericidal and acts by inhibiting the synthesis of protein in susceptible bacterial cells. It is effective primarily against gram-negative bacilli but does have some activity against gram-positive organisms. Neomycin is active *in vitro* against *Escherichia coli* and the *Klebsiella-Enterobacter* group. Neomycin is not active against anaerobic bowel flora. If susceptibility testing is needed, using a 30 mcg disc, organisms producing zones of 16 mm or greater are considered susceptible. Resistant organisms produce zones of 13 mm or less. Zones greater than 13 mm and less than 16 mm indicate intermediate susceptibility.

## INDICATIONS AND USAGE

### Hepatic coma (portal-systemic encephalopathy)

Neomycin sulfate has been shown to be effective adjunctive therapy in hepatic coma by reduction of the ammonia forming bacteria in the intestinal tract. The subsequent reduction in blood ammonia has resulted in neurologic improvement.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Neomycin Sulfate Oral Solution and other antibacterial drugs, Neomycin Sulfate Oral Solution should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

## CONTRAINDICATIONS

Neomycin sulfate oral preparations are contraindicated in the presence of intestinal obstruction and in individuals with a history of hypersensitivity to the drug.

Patients with a history of hypersensitivity or serious toxic reaction to other aminoglycosides may have a cross-sensativity to neomycin.

Neomycin sulfate oral solution is contraindicated in patients with inflammatory or ulcerative gastrointestinal disease because of the potential for enhanced gastrointestinal absorption of neomycin.

## WARNINGS

(see boxed WARNINGS)

Additional manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions.

The risk of hearing loss continues after drug withdrawal.

Aminoglycosides can cause fetal harm when administered to a pregnant woman.

Aminoglycoside antibiotics cross the placenta and there have been several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Although serious side effects to fetus or newborn have not been reported in the treatment of pregnant women with other aminoglycosides, the potential for harm exists. Animal reproduction studies of neomycin have not been conducted. If neomycin is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

## PRECAUTIONS

### General

Prescribing Neomycin Sulfate Oral Solution in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antibiotics, use of oral neomycin may result in overgrowth of non-susceptible organisms, particularly fungi. If this occurs, appropriate therapy should be instituted.

Neomycin is quickly and almost totally absorbed from body surfaces (except the urinary bladder) after local irrigation and when applied topically in association with surgical procedures. Delayed-onset, irreversible deafness, renal failure, and death due to neuromuscular blockade (regardless of the status of renal function) have been reported following irrigation of both small and large surgical fields with minute quantities of neomycin.

Cross-allergenicity among aminoglycosides has been demonstrated.

Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia gravis or parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

Small amounts of orally administered neomycin are absorbed through intact intestinal mucosa.

There have been many reports in the literature of nephrotoxicity and/or ototoxicity with the oral use of neomycin. If renal insufficiency develops during oral therapy, consideration should be given to reducing the drug dosage or discontinuing therapy.

An oral neomycin dose of 12 grams per day produces a malabsorption syndrome for a variety of substances including fat, nitrogen, cholesterol, carotene, glucose, xylose, lactose, sodium, calcium, cyanocobalamin and iron.

Oral administered neomycin increases fecal bile acid excretion and reduces intestinal lactase activity.

### Laboratory Tests

Patients with renal insufficiency may develop toxic neomycin blood levels unless doses are properly regulated. If renal insufficiency develops during treatment, the dosage should be reduced or the antibiotic discontinued. To avoid nephrotoxicity and eighth nerve damage associated with high doses and prolonged treatment, the following should be performed prior to and periodically during therapy: urinalysis for increased excretion of protein, decreased specific gravity, casts and cells; renal function tests such as serum creatinine, BUN or creatinine clearance; tests of the vestibulocochlearis nerve (eighth cranial nerve) function.

Serial, vestibular and audiometric tests should be performed (especially in high risk patients). Since elderly patients may have reduced renal function which may not be evident in the results of routine screening tests such as BUN or serum creatinine, a creatinine clearance determination may be more useful.

### Drug Interactions

Caution should be taken in concurrent or serial use of other neurotoxic and/or nephrotoxic drugs because of possible enhancement of the nephrotoxicity and/or ototoxicity of neomycin (see boxed WARNINGS).

Caution should also be taken in concurrent or serial use of other aminoglycosides and polymyxins because they may enhance neomycin's nephrotoxicity and/or ototoxicity and potentiate neomycin's neuromuscular blocking effects.

Oral neomycin inhibits the gastrointestinal absorption of penicillin V, oral vitamin B-12, methotrexate and 5-fluorourcil. The gastrointestinal absorption of digoxin also appears to be inhibited. Therefore, digoxin serum levels should be monitored.

Oral neomycin may enhance the effect of coumarin in anticoagulants by decreasing vitamin K availability.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
No long-term animal studies have been performed with neomycin to evaluate carcinogenic or mutagenic potential or impairment of fertility.

**Pregnancy**
Category D (see WARNINGS section)

**Nursing Mothers**
It is not known whether neomycin is excreted in human milk but it has been shown to be excreted in cow milk following a single intramuscular injection. Other aminoglycosides have been shown to be excreted in human milk. Because of the potential for serious adverse reactions from the aminoglycosides in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**
The safety and efficacy of oral neomycin in patients less than eighteen years of age have not been established. If treatment of a patient less than eighteen years of age is necessary, neomycin should be used with caution and the period of treatment should not exceed three weeks because of the absorption from the gastrointestinal tract.

**Information for Patients**
Patients should be counseled that antibacterial drugs including Neomycin Sulfate Oral Solution should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Neomycin Sulfate Oral Solution is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Neomycin Sulfate Oral Solution or other antibacterial drugs in the future.
Before administering the drug, patients or members of their families should be informed of possible toxic effects of the eighth nerve. The possibility of acute toxicity increases in premature infants and neonates.

**ADVERSE REACTIONS**
The most common adverse reactions to oral neomycin are nausea, vomiting, and diarrhea. The "Malabsorption Syndrome" characterized by increased fecal fat, decreased serum carotene and fall in xylose absorption has been reported with prolonged therapy. Nephrotoxicity, ototoxicity, and neuromuscular blockage have been reported (see boxed WARNINGS and PRECAUTIONS section).

**OVERDOSAGE**
Because of low absorption, it is unlikely that acute overdosage would occur with oral neomycin. However, prolonged administration could result in sufficient systemic drug levels to produce neurotoxicity, ototoxicity, and/or nephrotoxicity.
Hemodialysis will remove neomycin from the blood.

**DOSAGE AND ADMINISTRATION**
To minimize the risk of toxicity use the lowest possible dose and the shortest possible treatment period to control the condition. Treatment for periods longer than two weeks is not recommended.
**Hepatic coma**
For use as an adjunct in the management of hepatic coma, the recommended dose is 4-12 grams per day given in the following regimen:
1. Withdraw protein from diet. Avoid use of diuretic agents.

2. Give supportive therapy including blood products, as indicated.

3. Give NEO-FRADIN Oral Solution in doses of four to twelve grams of neomycin sulfate per day in divided doses. Treatment should be continued over a period of five to six days during which time protein should be returned incrementally to the diet.

4. If less potentially toxic drugs cannot be used for chronic hepatic insufficiency, neomycin sulfate in doses of up to four grams daily may be necessary. The risks for the development of neomycin induced toxicity progressively increase when the treatment must be extended to preserve the life of a patient with hepatic encephalopathy who has failed to fully respond. Frequent periodic monitoring of these patients to ascertain the presence of drug toxicity is mandatory (see PRECAUTIONS). Also, neomycin serum concentrations should be monitored to avoid potentially toxic levels. The benefits to the patient should be weighed against the risks of nephrotoxicity, permanent ototoxicity and neuromuscular blockade following the accumulation of neomycin in the tissues.

**HOW SUPPLIED**

NEO-FRADIN Oral Solution is available as a clear orange solution with a cherry flavor in 16 fl. oz and 2 fl. oz bottles containing 125 mg of neomycin sulfate (equivalent to 87.5 mg of neomycin) per five mL.

NDC 39822-0330-5 for 16 fl. oz.

NDC 39822-0330-2 for 2 fl. oz.

**Store at controlled room temperature 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].**

Manufactured for:

X-Gen Pharmaceuticals, Inc.

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